# Viral Hemorrhagic Fever (Ebola)

# 1. DISEASE REPORTING

## A. Legal Reporting Requirements

- 1. Health care providers and facilities: immediately notifiable to local health jurisdiction
- 2. Laboratories: **immediately notifiable to local health jurisdiction**; specimen submission requested positive specimens (2 business days) (Sections 3 and 4).
- 3. Local health jurisdictions: **immediately notifiable to Washington State Department of Health (DOH) Office of Communicable Disease Epidemiology (CDE)**.

## B. Local Health Jurisdiction Investigation Responsibilities

- 1. Immediately recommend infection control measures if agent is transmissible.
- 2. Immediately report all cases or potential cases to CDE: 1-877-539-4344 or 206-418-5500. Conduct a rapid assessment to determine whether bioterrorism is a possibility or if there is potential healthcare facility transmission.
- 3. Facilitate the transport of specimens for reference testing.
- 4. Determine the source of infection.
- 5. Identify other persons exposed and recommend monitoring as indicated.
- 6. Complete and enter the case report form: http://www.doh.wa.gov/Portals/1/Documents/5100/420-128-ReportForm-Ebola.pdf.

# 2. THE DISEASE AND ITS EPIDEMIOLOGY

#### A. Etiologic Agent:

Agents of viral hemorrhagic fever include four main families of viruses (filoviruses, arenaviruses, bunyaviruses, flaviviruses). Well-known agents are Ebola, Marburg and dengue viruses (also see Hantavirus and Yellow Fever guidelines). Ebola is enveloped and susceptible to hospital-grade disinfectants but may remain viable in organic matter (e.g., blood) on surfaces for several days. The viruses are potential agents of bioterrorism.

## **B.** Description of Illness

After abrupt onset of initial nonspecific symptoms of fever, headache, muscle and joint aches, and anorexia, after about 5 days disease progresses to watery diarrhea, vomiting and abdominal pain; there may be sore throat, desquamating rash, seizures, hiccups, or miscarriage. Damage to the liver, adrenal glands and spleen results in coagulopathy, hypotension, and impaired steroid synthesis. About half of cases have unexplained hemorrhage (petechiae, bruising, bleeding from mucous membranes or small injuries). Viremia peaks around 10 days from onset, also when most deaths occur. Up to 90% of cases are fatal due to multi-organ failure and shock. Convalescence is prolonged. Laboratory findings include platelets < 150,000; elevated hepatic transaminases (AST > ALT); elevated amylase. Differential includes malaria, typhoid, dengue, yellow fever, West Nile, chikungunya, other tropical infections, influenza, and non-infectious illnesses

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## C. Viral Hemorrhagic Fever in Washington

Washington has had no cases. In September 2014 Ebola was diagnosed in Texas associated with a West Africa outbreak. Rare cases of Ebola, Lassa and Marburg fever acquired elsewhere and imported into this country have not had subsequent transmission.

#### D. Reservoir:

Animals such as bats or rodents are common viral reservoirs. Outbreaks include Marburg in Democratic Republic of Congo (formerly Zaire) and Angola, Ebola in the DRC (location of the Ebola River) and southern Sudan, and dengue in various countries.

#### E. Modes of Transmission

Direct transmission from reservoir or secondarily infected animals occurs rarely; bush meat may be a risk. Person-to-person transmission of filoviruses such as Ebola then occurs by direct contact with body fluids or excreta (blood, urine, diarrhea, vomit, sweat, semen, milk) including percutaneous injection or mucous membrane contamination. Viremia starts within 1-2 day of onset, peaking at day 10. Ebola has spread by contact during funerals or handling human remains. There is no evidence of airborne spread.

# F. Incubation period

Incubation is 2-21 days, typically 3-10 days. The infectious dose is very low.

# G. Period of Communicability

Body fluids and excreta are infected from symptom onset, with very high viremia. Fomites have not been shown to be a source of exposure but virus may persist for days in organic debris including on bedding or medical equipment. Urine and semen remain infectious for weeks after recovery.

#### H. Treatment

Supportive care to maintain volume, electrolytes, blood pressure, and oxygenation.

#### 3. CASE DEFINITIONS

## A. Clinical description

Fever of greater than 38.6° C (101.5° F) for Ebola or greater than 40° C (104° F) for other agents of viral hemorhagic fever (VHF) AND additional symptoms such as severe headache, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained internal or external hemorrhage, or as applicable symptom of another suspected VHF agent (low platelets, rash, for arenavirus pharyngitis, retrosternal chest pain, or proteinuria).

# **B.** Epidemiologic risk factors

Ebola (or other communicable VHF): Within the 21 days before the onset of symptoms, contact with blood or other body fluids (including household, sexual, healthcare, and laboratory exposures) or human remains of a patient known to have or suspected to have EVD; residence in—or travel to—an area where EVD transmission is active; or direct handling of bats, rodents, or primates (or bush meat) from any disease-endemic area.

Other VHF: Within the 21 days before the onset of symptoms, residence in—or travel to—an area where VHF transmission is active including bite from implicated insect.

# C. Laboratory criteria for diagnosis

Any positive diagnostic evidence from a reference laboratory.

## D. Case classification (2014)

Person under Investigation (PUI) or Suspect: Fever AND other consistent clinical symptoms AND epidemiologic risk factors (e.g., travel to an affected area).

*Probable*: A PUI whose epidemiologic risk factors include high or low risk exposure.

Confirmed: A clinically compatible case with laboratory confirmation of VHF.

# 4. DIAGNOSIS AND LABORATORY SERVICES

## A. Laboratory Diagnosis

Clinical suspicion based on symptoms and risk of exposure is the most critical element for diagnosis of VHF. Initial presentation is nonspecific and may resemble other tropical illnesses, so testing for malaria should be considered. Hemorrhagic signs may not occur.

Commercial testing is available for dengue fever and chikungunya virus.

Early in the illness diagnostic tests for Ebola are polymerase chain reaction (PCR), antigen-capture enzyme-linked immunosorbent assay (ELISA), IgM ELISA, and viral isolation. Later in the disease course IgM and IgG antibodies can be tested. Deceased patients can be retrospectively tested by immunohistochemistry, PCR, or virus isolation.

Ebola laboratory testing must be performed by a reference laboratory such as the Washington State Public Health Laboratories (PHL) or Centers for Disease Control and Prevention (CDC). PHL will test for Ebola only with CDC pre-approval.

## B. Tests Available at the Washington State Public Health Laboratories (PHL)

PHL offers PCR testing to detect Ebola Zaire virus (2014 outbreak strain). Negative PCR results do not preclude Ebola Zaire virus infection and should not be used as the sole basis for patient management decisions, particularly early in the illness. Presumptive positive PCR results require additional confirmatory testing by the CDC. **Prior to submitting specimens, obtain approval from Office of Communicable Disease Epidemiology (206-418-5500 or 877-539-4344).** To be tested, the patient should meet one of the three case classifications (see Section 3).

Note that PHL require all clinical specimens have two patient identifiers, a name **and** a second identifier (e.g., date of birth) both on the specimen label and on the submission form. Due to laboratory accreditation standards, specimens will be rejected for testing if not properly identified. Also include specimen source and collection date.

# C. Specimen Collection

For infection control measures related to specimen collection, see Section 5C.

Collect duplicate specimens of whole blood (2 EDTA purple top <u>plastic</u> tubes  $\geq$  4 ml each), refrigerate, transport cold. Take specimens when a symptomatic patient is seen by a healthcare facility and is suspected of having an EVD exposure; if symptom onset is

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within 3 days, a subsequent specimen may be required to completely rule out EVD. Fresh tissue specimens of affected organs and prior frozen specimens are also acceptable.

Specimens for viral hemorrhagic fever <u>must be shipped as Category A.</u> PHL will provide shipping boxes. For guidance see: <a href="http://www.cdc.gov/vhf/ebola/hcp/interimguidance-specimen-collection-submission-patients-suspected-infection-ebola.html">http://www.cdc.gov/vhf/ebola/hcp/interimguidance-specimen-collection-submission-patients-suspected-infection-ebola.html</a>

All specimens should be submitted to PHL with a completed Serology/Virology form: <a href="http://www.doh.wa.gov/Portals/1/Documents/5230/302-017-SerVirHIV.pdf">http://www.doh.wa.gov/Portals/1/Documents/5230/302-017-SerVirHIV.pdf</a>

# 5. ROUTINE CASE INVESTIGATION

Viral hemorrhagic fever (VHF) agents are potential agents of bioterrorism. Immediately report any suspect VHF cases to Office of Communicable Disease Epidemiology (206-418-5500 or 877-539-4344).

For the most recent Ebola outbreak information from Centers for Disease Control and Prevention check: <a href="http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/whats-new.html">http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/whats-new.html</a>

Immediately interview the case, suspect or confirmed, and others who may be able to provide pertinent information.

## A. Evaluate the Diagnosis

In a healthcare facility, place patient in appropriate precautions if viral hemorrhagic fever (VHF) is suspected unless another cause of symptoms has been identified. Review the clinical presentation, exposures, and laboratory findings.

Compatible symptoms are fever (> 38.6° C or 101.5° F), severe headache, muscle pain, abdominal pain, vomiting, diarrhea, and in about half of patients unexplained hemorrhage (petechiae, bruising, oozing from cuts, mucosal bleeding). Gastrointestinal symptoms start around day 5 and there may also be a diffuse erythematous maculopapular rash that desquamates. Other symptoms may include sore throat, shortness of breath, chest pain, confusion, seizures, conjunctival injection, hiccups, or miscarriage.

Supportive laboratory findings include thrombocypotenia (platelets < 150,000) and elevated hepatic transaminases (AST > ALT). If disseminated intravascular coagulation develops, prothrombin (PT) and partial thromboplastin (PTT) times are prolonged. Leukopenia, elevated amylase, and proteinuria may occur.

Consider testing a febrile patient for malaria, the most common cause of fever in travelers returning from the affected region or, if indicated, other infections such as typhoid fever, other bacterial or parasitic cause of diarrhea, meningococcemia, or pneumonia.

Laboratory testing for transmissible viral hemorrhagic fever must be performed by a reference laboratory such as the Washington State Public Health Laboratories (PHL). Facilitate transport of specimens to PHL for confirmatory testing (see Section 4).

#### **B.** Identify Potential Sources of Infection

Identify potential sources in the prior 21 days, including travel to currently affected countries or previous endemic areas, or contact with a person having such travel. High risk exposures for viral hemorrhagic fever (VHF):

- percutaneous or mucous membrane exposure to VHF-contaminated blood, body fluids or excreta
- direct skin contact with or exposure to blood or body fluids of, a VHF patient without appropriate personal protective equipment (PPE)
- processing blood or body fluids of a confirmed VHF patient without appropriate PPE or standard biosafety precautions
- direct contact with a dead body without appropriate PPE in a country where an VHF outbreak is occurring

Exposures with low risk for viral hemorrhagic fever:

- household member or person having brief casual contact (e.g., shaking hands) with VHF case, unless known high risk exposure
- providing patient care or being present in a patient care areas for a prolonged period without appropriate use of PPE, unless known high risk exposure
- other close contact with a VHF patient in healthcare or community settings

# No Known Exposure:

 having been in a country in which a VHF outbreak has occurred within the past 21 days and having had no known exposures; while in any known endemic area handled bat, rodent, primate, or game (bush) meat

## C. Evaluate for testing

Include a full travel history with any test requests.

# **Testing for Ebola virus disease:**

Testing is <u>recommended</u> for the following patients (also consider testing for malaria or other tropical infections as indicated); optionally other situations may be tested if there is no other consistent diagnosis. Compatible symptoms are intense weakness, muscle pain, severe headache, vomiting, diarrhea, impaired kidney and liver function, and internal or external bleeding. Supportive abnormal blood work would include platelet count < 150,000 and AST/ALT elevation (may also be prolonged AT/ATT). Test patients with:

- High risk exposure AND Either fever of greater than 38.6° C or 101.5° F or compatible symptoms (above) without fever
- Low risk exposure AND Either fever of greater than 38.6° C or 101.5° F or compatible symptoms without fever AND Abnormal laboratory test results (optional testing if laboratory test results normal or unknown)
- Optional testing: No known exposure AND Fever AND Other compatible symptoms AND Abnormal laboratory test results AND Absence of alternative diagnosis

## Testing for other agents of viral hemorrhagic fever:

Test as indicated by symptoms and exposure history for dengue or other agent of VHF.

#### **D.** Patient Management

Experimental medications may be available to treat Ebola virus disease. DOH will consult with Centers for Disease Control and Prevention for each case. Medical treatment of a case

includes providing intravenous fluids (IV), balancing electrolytes, maintaining oxygen status and blood pressure, addressing organ failure (e.g., providing dialysis) and treating other infections if they occur. For transmissible agents, always follow infection control measures.

# E. Infection Control/Case Management for Transmissible VHF Agents (e.g., Ebola)

- 1. Hospitalized patients should be cared for in a single patient room (with a private bathroom) with the door closed, and transport within the facility minimized. The room should have a mattress and pillow with plastic covers that are impermeable to fluids. Do not use a carpeted room. Remove upholstered furniture and decorative curtains.
- 2. Log all persons entering the room and minimize staff authorized to enter. Avoid entry of visitors into the patient's room. Exceptions may be considered on a case by case basis for those who are essential for the patient's wellbeing.
- 3. Require use of personal protective equipment (PPE) for patient care and environmental cleaning including gloves, gown (fluid resistant or impermeable), eye protection (goggles or face shield), and facemask, at a minimum.
- 4. If copious amounts of body fluids or excreta are present in the environment, require use of additional PPE including but not limited to double gloving, disposable shoe covers, and leg coverings.
- 5. Instruct staff in hand hygiene and the proper use of PPE including safe removal and disposal. Consider a buddy system for donning and removing PPE.
- 6. Use dedicated medical equipment, preferably disposable, and clean and disinfect any non-disposable equipment after use.
- 7. Limit use of needles and other sharps, and handle used sharps with extreme care when disposing of them in puncture-proof sealed containers.
- 8. Minimize laboratory testing, and notify the laboratory that incoming specimens are from a suspect or confirmed VHF case.
- 9. Minimize aerosol-generating procedures (AGP) for the patient, and conduct such procedures with minimal required staff and no visitors present in an airborne infection isolation room (AIIR), if available. During AGPs, staff should use appropriate PPE including at least a fit-tested N95 filtering facepiece respirator. The procedure should be followed by environmental cleaning of the room and equipment by trained staff using appropriate PPE (see items 3 and 4 above).
- 10. If inadvertent exposure occurs during patient care, staff should immediately wash or irrigate the affected area, report to occupational health, be assessed for all appropriate pathogens (e.g., HIV, HBV, HCV), and initiate monitoring (See Section 6 below).
- 11. Move patients between healthcare facilities only by air medical transport.
- 12. After discharge, patient should be informed that urine and semen may contain virus for up to 60 days during convalescence. The discharged patient may use toilets with routine sewer disposal of bodily fluids.
- 13. Only personnel trained in handling infected human remains, and wearing PPE, should touch, or move, any VHF-infected remains. Minimize handling, avoid embalming and

autopsies on patients who die of Ebola; if an autopsy is necessary, consult with Office of Communicable Disease Epidemiology (206-418-5500 or 877-539-4344). Cremate remains or bury promptly in a hermetically sealed casket.

## F. Identify Potentially Exposed Persons for Transmissible VHF Agents (e.g., Ebola)

Contact traceback and management will be done in coordination with the Centers for Disease Control and Prevention (CDC). Contact tracing is key for control. Immediately institute identification of potentially exposed persons for evaluation of level of risk and appropriate public health actions such as fever watch or home quarantine for 21 days (maximum incubation period). See: <a href="http://www.cdc.gov/vhf/ebola/pdf/contact-tracing.pdf">http://www.cdc.gov/vhf/ebola/pdf/contact-tracing.pdf</a>

- 1. Identify persons with shared the initial exposure of the case patient, such as cotravelers or co-workers.
- 2. Identify contacts of the case patient, including household members, healthcare workers, and other patients being seen at the same time in the healthcare facility as the VHF case.
- 3. Evaluate above persons with risk exposures for symptoms. If symptomatic, manage as a Person Under Investigation (Section 5). If asymptomatic, see Section 6.

## G. Environmental Measures for Transmissible VHF Agents

Potentially contaminated materials include anything containing body fluids or excreta including medical devices, syringes, laboratory testing equipment, bedpans, textiles and laundry, and utensils and dishware. Do daily environmental cleaning and disinfection of a patient room for all surfaces and reusable equipment potentially contaminated with body fluids or excreta, and high touch areas such as bed rails, tables, and counters. Use a U.S. Environmental Protection Agency (EPA)-registered hospital disinfectant with a label claim for a non-enveloped virus (e.g., norovirus, rotavirus, adenovirus, poliovirus) to disinfect environmental surfaces in rooms of patients with suspected or confirmed communicable VHF infection. Use other methods such as autoclaving or incineration as appropriate. To reduce exposure to potentially contaminated textiles while laundering, discard all linens, non-fluid-impermeable pillows or mattresses, and textile privacy curtains as a regulated medical waste. Dishes and cutlery should also be discarded.

Staff doing environmental cleaning and disinfection should wear appropriate PPE, at a minimum, disposable gloves, gown (fluid resistant/ impermeable), eye protection (goggles or face shield), and facemask to prevent exposure to cleaning contamination, chemicals, and splashes or spatters; consider using additional barriers (e.g., shoe and leg coverings) if needed. Use face protection (face shield or facemask with goggles) when doing tasks that can generate splashes such as liquid waste disposal. Follow standard procedures, per hospital policy and manufacturers' instructions, for cleaning and/or disinfection. Put disposable materials in leak-proof containers and discard as regulated medical waste. To minimize contamination of the exterior of a bag, place the bag in a rigid waste receptacle designed for this use. Sanitary sewers will safely dispose of patient wastes. Seal bodies in leak-proof containers and cremate or bury promptly.

# 6. MANAGING SPECIAL SITUATIONS

# Managing persons potentially exposed to transmissible VHF agents.

Potentially exposed persons will be managed in coordination with CDC. Obtain information about travel and exposure to VHF patients, including details of exposures, date of last exposure, and exposure to healthcare settings or reservoir animals.

- 1. Evaluate the exposure as high risk, low risk, or no known exposure. See: <a href="http://www.cdc.gov/vhf/ebola/pdf/ebola-algorithm.pdf">http://www.cdc.gov/vhf/ebola/pdf/ebola-algorithm.pdf</a>
  - a. High risk: percutaneous or mucous membrane exposure to body fluids or excreta of a VHF case; direct VHF patient care or laboratory work without personal protective equipment (PPE); funeral rite or other direct contact with human remains in affected country without PPE
  - b. Some risk: household member or other casual contact without high risk exposure; direct VHF patient care or environmental cleaning with PPE and no known exposure; other close contact of VHF patient in healthcare setting
  - c. No known risk: in affected country but without high or low risk exposure; potential exposure in a known endemic area (e.g., contact with a bat, rodent, primate, or bush meat)
- 2. Initiate evaluation and monitoring. For a healthcare facility checklist see: <a href="http://www.cdc.gov/vhf/ebola/pdf/checklist-patients-evaluated-us-evd.pdf">http://www.cdc.gov/vhf/ebola/pdf/checklist-patients-evaluated-us-evd.pdf</a>
  - a. High risk and consistent symptoms: initiate infection control measures in a healthcare setting (including PPE for providers and environmental cleaning), evaluate, test if indicated; move only by air medical transport; if not a suspect case initiate conditional release<sup>1</sup> and controlled movement<sup>2</sup> including travel restrictions until 21 days after last exposure
  - b. High risk and not symptomatic: Initiate conditional release<sup>1</sup> and controlled movement<sup>2</sup> including travel restrictions until 21 days after last exposure
  - c. Low risk and consistent symptoms: initiate infection control measures in a healthcare setting (including PPE for providers and environmental cleaning), evaluate, test if indicated; move only by air medical transport; if not a suspect case initiate conditional release<sup>1</sup> and controlled movement<sup>2</sup> including travel restrictions until 21 days after last exposure
  - d. Low risk and asymptomatic: Initiate conditional release<sup>1</sup> and controlled movement<sup>2</sup> including travel restrictions until 21 days after last exposure
  - e. No known risk: Initiate self-monitoring until 21 days after last exposure

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<sup>&</sup>lt;sup>1</sup> Conditional release: Monitoring by public health authority; twice-daily self-monitoring for fever; notify public health authority if fever or other symptoms develop

<sup>&</sup>lt;sup>2</sup> Controlled movement: Notification of public health authority; no travel by commercial conveyances (airplane, ship, and train), local travel for asymptomatic individuals (e.g. taxi, bus) should be assessed in consultation with local public health authorities; timely access to appropriate medical care if symptoms develop

If home quarantine is being considered, ask the contacts about support requirements including dietary needs, prescription and non-prescription medications, personal care supplies, child care supplies and pet care.

If home quarantine is not possible, identify another location where the contact can stay during the full period of observation (21 days from last exposure).

When recommending monitoring of an asymptomatic person, develop an individual plan for steps if a fever or other consistent symptoms develop, including:

- Receiving healthcare facility ability to evaluate person in a private room with a door
- Receiving facility availability of appropriate PPE for staff 24/7
- Notification point of contact at the facility 24/7
- Facility's laboratory preparation for receiving specimens and testing in a closed system
- Family plan, such as child care if person is a single parent, or pet care
- Means of transport to the facility to minimize exposing others (e.g., patient to drive self; driver to wear eyewear and avoid skin contact with patient)

# 7. ROUTINE PREVENTION

#### A. Prevention Recommendations

Except for yellow fever, there are no vaccines for viral hemorrhagic fever agents.

Meticulous attention to personal protective equipment (PPE) and environmental cleaning during patient care are essential to prevent exposure to transmissible VHF agents. Particular care should be taken when removing PPE to avoid contamination.

## 8. RESOURCES

As of September, 2014, recommendations and guidances for Ebola virus disease are changing rapidly. Check the CDC website for the most current information.

Main document site: <a href="http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/whats-new.html">http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/whats-new.html</a>
Public health Ebola preparedness:

http://www.cdc.gov/vhf/ebola/pdf/ems-checklist-ebola-preparedness.pdf

http://www.cdc.gov/vhf/ebola/outbreaks/preparedness/planning-tips-top10.html

http://www.cdc.gov/vhf/ebola/pdf/contact-tracing.pdf

Case definition: http://www.cdc.gov/vhf/ebola/hcp/case-definition.html

Clinician information:

http://www.cdc.gov/vhf/ebola/hcp/clinician-information-us-healthcare-settings.html

Hospital infection control:

 $\underline{http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html}\\ \underline{http://www.cdc.gov/vhf/ebola/hcp/environmental-infection-control-in-hospitals.html}$ 

Hospital checklist:

http://www.cdc.gov/vhf/ebola/pdf/coalition-checklist-ebola-preparedness.pdf

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#### Clinical laboratories

http://www.cdc.gov/vhf/ebola/hcp/safe-specimen-management.html

http://www.cdc.gov/vhf/ebola/hcp/select-agent-regulations.html

http://www.cdc.gov/vhf/ebola/hcp/interim-guidance-specimen-collection-submission-patients-suspected-infection-ebola.html

Emergency Medical Services checklist:

http://www.cdc.gov/vhf/ebola/hcp/interim-guidance-emergency-medical-services-systems-911-public-safety-answering-points-management-patients-known-suspected-united-

states.html

http://www.cdc.gov/vhf/ebola/pdf/ems-checklist-ebola-preparedness.pdf

## Monitoring exposed persons:

http://www.cdc.gov/vhf/ebola/hcp/monitoring-and-movement-of-persons-with-exposure.html Humanitarian aid organizations and workers:

http://wwwnc.cdc.gov/travel/page/advice-humanitarian-aid-organizations-ebola

http://wwwnc.cdc.gov/travel/page/humanitarian-workers-ebola

#### Colleges and universities:

http://wwwnc.cdc.gov/travel/page/advice-for-colleges-universities-and-students-about-ebola-in-west-africa

Airline and airline crew resources:

http://www.cdc.gov/quarantine/air/reporting-deaths-illness/index.html

#### Air medical transport:

http://www.cdc.gov/vhf/ebola/hcp/guidance-air-medical-transport-patients.html

#### APHA Ebola chapter:

http://www.apha.org/~/media/files/pdf/pubs/ccdm\_ebola.ashx

## **ACKNOWLEDGEMENTS**

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## **UPDATES**

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